Issues in Emerging Health Technologies

Ezetimibe for Lowering Blood Cholesterol

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Summary

- ✓ **Ezetimibe is the first drug in a new class called cholesterol absorption inhibitors.**
- ✓ **There is no evidence that ezetimibe will reduce rates of death or hospitalization.**
- ✓ **When it is taken alone or when it is added to existing statin therapy, ezetimibe can reduce serum cholesterol in patients who have an increased risk of future coronary artery disease.**
- ✓ **The safety and tolerability of ezetimibe alone or combined with a statin has not been established in trials beyond 12 weeks.**

The Technology

Ezetimibe is a 2-azetidinone that can reduce the rate of cholesterol absorption by the human small intestine. This is associated with reduced fasting total cholesterol (TC) and low-density lipoprotein (LDL-C) levels in individuals with mild to moderate elevations of LDL-C (≥3.4 but ≤4.7 mmol/L).[1]

Regulatory Status

In May 2003, drug manufacturer Merck Frosst-Schering Pharma, G.P. received Canadian approval to market ezetimibe (Ezetrol™) alone or with a statin, as an adjunct to diet, to certain individuals with high blood cholesterol.[2] It can be combined with a statin for patients with a genetic predisposition to severely high levels of LDL-C, called homozygous familial hypercholesterolemia (FH).[2] In the US, ezetimibe is marketed under the brand name Zetia™.

Patient Group

An elevated LDL-C level or TC/high-density lipoprotein fraction (TC/HDL-C) ratio are two (of several) factors that predict future coronary artery disease (CAD). The heterozygous form and more serious homozygous form of FH occur in 1/500 people and 1/1,000,000 people respectively.[3] These patients experience complications from CAD earlier in life than the rest of the population.

Complications of CAD, including sudden death, myocardial infarction and angina pectoris, accounted for 19.4% of all deaths in Canada in 1999.[4] In 2000-2001, they caused 25% of all hospitalizations in men and women over the age of 50.[4]

Current Practice

Therapy begins after an assessment of future CAD risk (low, moderate, high). Dietary and lifestyle modifications are the initial focus. If these are unsuccessful or the patient is at high risk (e.g., CAD present), more aggressive therapy, including drug therapy, is suggested.

Current guidelines suggest that a statin be used as the first line of therapy.[5,6] If targeted lipid levels are unachieved, additional strategies may include intensified lifestyle therapy, increased dosage of the statin, or combination of the statin with a bile acid sequestrant (cholestyramine; colestipol; colesevelam, which is unavailable in Canada), a cholesterol absorption inhibitor (ezetimibe), niacin, a fibrate (gemfibrozil, bezafibrate, fenofibrate) or salmon oil.[5,6] Individuals at very high risk who are resistant to medical therapy may require plasma apheresis.

Table 1: Randomized placebo-controlled parallel group trials

Therapy (number of RCTs/number of patients)	Dose (duration)	Avg age	% high risk[a] (% CHD)	Mean baseline LDL-C[b]	Mean LDL-C at end of treatment (95% CI)	Mean baseline HDL-C/ TC ratio	Mean HDL-C/ TC at end of treatment (95% CI)
Ezetimibe[9,14-16] monotherapy[c] (2/1,719)	10 mg qam (12 weeks)	58.1[d]	29.6[c] (5.8%)[d]	4.3 mmol/L	3.5 (3.4, 3.6)	4.8	4.1 (NR)[e]
Ezetimibe[10] added to existing statin (1/769)	10 mg qam (12 weeks)	60.0	100 (≤68%)[f]	3.6 mmol/L	2.8 (2.7, 2.9)	4.6	3.9 (3.8, 4.0)

[a] according to National Cholesterol Education Program (Adult Treatment Panel II)[17]; [b] a direct method for LDL-C was reported; [c] based on pooled analyses as individual trial data were unavailable; [d] approximated from supplementary information; [e] ($p \leq 0.01$); [f] these patients had known CHD or diabetes; Avg=average; CHD=coronary heart disease; qam=every morning; NR=not reported.

The Evidence

None of the available randomized controlled trial (RCT) evidence[7-14] is of sufficient duration or statistical power to detect differences in patient-oriented outcomes such as death and hospitalization. Characteristics of trials where patients with elevated cholesterol (LDL-C≥3.4 mmol/L, triglyceride (TG)≤3.95 mmol/L) are randomized to take ezetimibe or a placebo are shown in Table 1.

The cholesterol-lowering effect is supported by four 12-week factorial RCTs (n=2,742) comparing ezetimibe, statin (atorvastatin, lovastatin, simvastatin, pravastatin), ezetimibe plus statin and placebo in adults with elevated cholesterol (LDL-C 3.8 to 6.5 mmol/L, TG≤3.95 mg/dL).[7,8,13,18] Ezetimibe alone did not lower cholesterol as much as a statin, but when it was combined with a statin, the effect was greater than that of either ezetimibe or a statin alone.[19] The size of this effect varies with the dosage and choice of statin.

Familial hypercholesterolemia: One RCT[11,19] (n=50) compared ezetimibe or placebo added to atorvastatin or simvastatin (40 mg or 80 mg) in individuals with genetically or clinically diagnosed homozygous FH and elevated cholesterol (LDL-C≥2.6 mmol/L, TG≤3.95 mmol/L while taking atorvastatin or simvastatin 40 mg). Compared with high-dose (80 mg) atorvastatin or simvastatin therapy, ezetimibe 10 mg combined with 40 mg or 80 mg of either statin further reduced LDL-C (14.1%, 95% CI: 4 to 24) without significantly (p=0.27) reducing TC/HDL-C (6.4%, 95% CI: −10.3% to 23%).

Adverse Effects

Ezetimibe alone or added to a statin did not significantly alter serious adverse event rates or withdrawal rates due to adverse events in eight- and 12-week trials.[15] Liver function tests and monitoring are recommended when ezetimibe is combined with a statin, as an increase in the enzyme markers of liver damage was observed.[2] Recent cases of angioedema and rash have been reported.[20]

Administration and Cost

Ezetimibe 10 mg is priced by the manufacturer at $1.58 per tablet. It can be taken once daily, alone or with a statin.

Concurrent Developments

Other inhibitors of cholesterol absorption being investigated include inhibitors of cholesteryl ester transfer protein, acyl coenzyme A:cholesterol acyltransferase, ileal bile acid transport protein and microsomal TG transfer protein; phytosterols and modified phytosterols. Newer formulations of niacin and niacin-statin combination products are marketed outside Canada.[21]

Rate of Technology Diffusion

Based on marketing experience in the US[22] and endorsements in newer dyslipidemia guidelines,[5] rapid diffusion is likely. In Canada, rapid uptake of new lipid-lowering agents has been significant based on short-term data,[23,24] despite a demonstrated reduction in CAD death and morbidity with niacin, cholestyramine and some statins.

Relevant alternatives to ezetimibe include niacin, cholestyramine, fibrates and higher-dose or increased-potency statin therapy. These will likely be viewed as less attractive because of concerns about side effects, patient tolerability and compliance.

Implementation Issues

Trials to assess safety and tolerability beyond 12 weeks are ongoing.[15,25] Unknown serious adverse drug reactions more frequently emerge after marketing approval.[26]

Cost-effectiveness analyses speculating on reductions in death and morbidity may be based on short-term RCT outcomes. These results can overestimate what is achievable in practice.[27]

Producing more lipid target "responders" with ezetimibe will be appealing, despite the unknown consequences and increased costs. Recent evidence from statin trials suggests that potential benefits could depend on overall CAD risk and be less reflective of cholesterol levels.[28-30] The theory that larger cholesterol reductions result in larger reductions in death and hospitalization is being tested with statins.[31]

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